REMARKS

Applicant submits that the amendments herein are fully supported in the present specification as filed, are clearly editorial in nature and add no new matter. Therefore, entry of the present amendment is proper, and is respectfully requested. Applicant also notes that many claims are being canceled, thereby reducing issues that may be raised during appeal.

A Petition for Extension of Time is being concurrently filed with this Amendment. Thus, this Amendment is being timely filed.

Applicant respectfully requests the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims

Claims 27-30 are pending in the application. In the present Amendment, claims 27-29 have been amended such that "Silymarin" and "Carbopol" are no longer capitalized. Also, withdrawn claims 1-6 and 10-16 are canceled with prejudice or disclaimer of the subject matter contained therein. Applicant reserves the right to file any divisional directed to such canceled subject matter.

No new matter has been added with the present amendments as these changes are clearly minor in character.

Based on the above comments, entry of the present claim amendments is respectfully requested.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

Substance of the Interview

Applicant thanks the Examiner and Primary Examiner for their time, helpfulness and courtesies extended to Applicant and Applicant's representatives during the Interview of October 30, 2008. The assistance of the Examiners in advancing prosecution of the present application is greatly appreciated. In compliance with M.P.E.P. § 713.04, Applicant submits the following remarks.

The Interview Summary form (dated October 30, 2008) amply summarizes the discussions at the Interview. Various ways of addressing the prior art rejection were discussed, including the suggestion of Applicant filing a Rule 132 Declaration explaining the features of the invention in view of the cited references.

Issues under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 27-30 under 35 U.S.C. § 103(a) as being obvious over **Bibbs et al. '128** (U.S. Public. No. 2004/0006128 A1), in view of **Soto et al.** (*Comp. Biochem. Physiol.*, Vol. 119C, No. 2, pp. 125-129 (1998)) and **Coote et al. '034** (U.S. Public. No. 2004/0167034 A1). Applicant respectfully traverses for reasons of record and for the reasons stated herein.

Applicable U.S. Case Law

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an

obviousness analysis. The four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 set forth some rationales that were set established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Here, the Examiner has not appropriately resolved the *Graham* factors, including ascertaining the differences between the prior art and the claims that are at issue, and the rationale in combining the cited references is improper.

A composition for lowering blood glucose level does not entail that β-pancreatic cells are ***regenerated***

Applicant respectfully maintains that it is quite elemental that lowering blood glucose does not lead to the regeneration of the endocrine pancreatic function. To support such argument, Applicant herein submits a Declaration under 37 C.F.R. § 1.132. Attached to the Rule 132 Declaration is an article by C. Soto *et al.* (the inventor plus others) titled "Silymarin induces recovery of pancreatic function after alloxan damage in rats," *Life Sciences*, Vol. 75, pp. 2167-2180 (2004). As seen from the discussion in the Rule 132 Declaration, one of skill in the art would understand that lowering blood glucose does not lead to the regeneration of the endocrine pancreatic function, and that the presently claimed invention is directed to a use that is not

explicitly or inherently disclosed in the cited references. The experimental testing in the *Life Sciences* (2004) article, and as discussed in the Rule 132 Declaration, show that silymarin recovered the endocrine pancreatic tissue in alloxan-induced diabetes mellitus affected rats at both structural and functional levels. For instance, the pancreatic histological examinations as depicted Figures 4A-4C of the *Life Sciences* (2004) article show how silymarin treatment can lead to regeneration of the tissue such that it becomes indistinguishable from the tissue of the normal, non-treated control groups.

Regarding the cited combination of references, Applicant notes that Bibbs et al. '128 only mentions that blood glucose is lowered but does not cite that β-pancreatic cells are regenerated. Applicant further notes that the lowering of blood glucose in Bibbs et al. '128 does not entail β-pancreatic cells are regenerated.

Similarly in the Office Action, the Examiner asserts that Soto et al. teaches that silymarin has shown protective effects against the oxidative peroxidation of cells. The applicant sustains though that Soto et al. shows silymarin's non-regenerative protective effect, there is still no disclosure of the instant invention. Applicant further notes that Soto et al. shows that silymarin has a protective effect on pancreatic lipid peroxidation with the recovery of the beta cell function. However, Applicant respectfully maintains that the pancreatic lipid peroxidation is not regenerative.

Applicant also notes that the study in Soto et al. suggests the induction of diabetes mellitus by alloxan in rats may be prevented by silymarin administration. However, the applicant sustains that the prevention mentioned above does not favor regeneration.

The Examiner further asserts that Coote et al. '034 teaches that flavonoids demonstrate free radical scavenging properties. But as explained above, Applicant respectfully maintains that the scavenging of free radicals is not regenerative.

Also, Applicant respectfully refers the Examiner to one of the attachments to the Rule 132 Declaration - - **Chapter 60** of "Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Pancreas," of *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition. Chapter 60 of *The Pharmacological Basis of Therapeutics* discusses and differentiates extensively what entails the regeneration of the endocrine pancreatic function and what entails lowering blood glucose.

A bioflavonoid that can be used to lower blood glucose does not necessarily regenerate endocrine pancreatic function

Regarding the cited Coote et al. '034 reference and the comments in the Office Action, Applicant respectfully maintains that just because a bioflanovoid can be used to lower glucose does not necessarily mean that it is inherent that the bioflanovoid will have a regenerator pancreatic function. In this respect, Applicant notes that there is a great of variety of existing bioflavonoids found in nature with very many different pharmacological effects. Applicant also refers the Examiner to page 7 of the attached Rule 132 Declaration which refers to a scientific article by Andrade-Cetto *et al.* from the *Journal of Ethno-Pharmacology*. The Andrade-Cetto *et al.* article depicts how many different types of bioflavonoids are found in Mexican plants, which have different pharmacological effects and that not all flavonoids can have the ability to lower the blood glucose or regenerate endocrine pancreatic function.

In this regard, combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 483-84 (1966); *see also* M.P.E.P. § 2143. Accordingly, one of skill in the art would understand that lowering blood glucose does not lead to the regeneration of the endocrine pancreatic function, and that the presently claimed invention is directed to a use that is not explicitly or inherently disclosed in the cited references of Bibbs *et al.* '128, Soto *et al.* (1998) and Coote *et al.* '034.

Applicant maintains this rejection is improper for reasons of record

Bibbs et al. '128 discloses in paragraph [0013] an anti-diabetic activity (without indicating what type of diabetes is being treated) of the flavonoid **isovitexin**. Bibbs et al. '128 disclose in paragraphs [0042] through [0046] the mechanism of action of isovitexin in reducing the glucose concentration in the organism. There is simply no mention or reference whatsoever made in Bibbs et al. '128 of the using of silymarin and carbopol. The only mention of carbopol in Bibbs et al. '128 is a passing reference in a laundry list in paragraph [0064] that a dragee core may optionally contain "gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures". The rationale should be made explicit, *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), and the Examiner must interpret the reference as a whole and cannot pick and choose only those selective portions of the reference which support the Examiner's position. *In re Fine,* 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the

claimed invention."). There is no suggestion in Bibbs et al. '128 of selectively choosing carbopol to be used in a composition. Further, there is no rationale, suggestion, or motivation, to one skilled in the art to selectively replace isovitexin with silymarin based on such disclosure. Despite the fact that silymarin is a bioflavonoid, its choice as a regenerator of endocrine pancreatic function is not obvious due to the great variety of existing bioflavonoids found in nature and their diversity in chemical structure. The Examiner cites Soto et al. and Coote et al. '034 to account for the deficiencies of Bibbs et al. '128.

Soto et al. discloses the effect of silymarin as an antioxidant and that the reduction of blood glucose observed is due to the capture of free radicals by which cell damage of pancreatic tissue was prevented. Soto et al. thus highlights the protective effect of silymarin in diabetes mellitus. The experimentation in Soto et al. did not consider a regenerative effect. Applicant is aware of the cited Soto et al. reference, as this reference is even discussed in Applicant's specification at page 2, lines 19-22. In addition, the instant invention is directed to a composition containing a combination silymarin and carbopol. There is no suggestion in Soto et al. of such a combination. Nor is there any disclosure or suggestion in Soto et al. regarding any regenerative activity. While Soto et al. is used prophylactically to prevent the damage that could result from alloxan, the subject matter of the instant claims is directed to the curative activity with damaged pancreatic cells.

Still, in the Office Action, the Examiner maintains that the claimed regenerative effect is an inherent characteristic and thus disclosed in the cited references (see Office Action at, e.g., page 9, second full paragraph). Applicant respectfully notes that the present claims are directed to methods, and that a known compound can have a new use (e.g., minoxidil can be used to grow

hair and not just treating high blood pressure). Further, the instantly claimed combination is not disclosed in any one of the cited references. The USPTO has basically pulled together several references together to reject the instant method claims that recite a combination of Silymarin and Carbopol. Under *KSR*, there is no proper rationale or reason to do so, and Applicant respectfully maintains that the cited combination of references is not what one of ordinary skill in the art would do.

Accordingly, Applicant respectfully maintains that the prior art references do not, in combination, disclose or suggest a method of recovering endocrine pancreatic function with the oral administration of a composition comprising silymarin and carbopol as instantly claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

A full and complete response has been made to all issues as cited in the Office Action. Applicant has taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicant respectfully requests that a timely Notice of Allowance issue for the present case.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, Ph.D., Reg. No. 40,069, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: NOV 2 6 2008

Respectfully submitted,

By #41,501
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Attachment:

- Declaration under 37 C.F.R. § 1.132 with attached (1) article by C. Soto *et al.*, "Silymarin induces recovery of pancreatic function after alloxan damage in rats," *Life Sciences*, Vol. 75, pp. 2167-2180 (2004) and (2) Chapter 60 of "Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Pancreas," of *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition